

BIOGRAPHICAL NOTES BEARING ON KOCH,  
EHRLICH, BEHRING AND LOEFFLER, WITH  
THEIR PORTRAITS AND LETTERS FROM THREE  
OF THEM.

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(With Portrait-plates 26-29, two Letters and a Signature in facsimile.)

(*From the Molteno Institute for Research in Parasitology,  
University of Cambridge.*)

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THE four distinguished German men of science to whom the following biographical notes relate: Robert Koch (1843-1910), Paul Ehrlich (1854-1915), Emil von Behring (1854-1917), and Friedrich Loeffler (1852-1915), form a group of singular interest because of the relations that existed between them and the various problems to the solution of which they devoted their remarkable talents and energies. Each of them has left an indelible mark upon the annals of research and discovery in relation to infective diseases of man and animals, their etiology, prevention and cure. If it were at all possible to reckon up the sum of human and animal lives that they have saved from premature extinction through their collective efforts, direct and indirect, the total would attain gigantic proportions. Mankind should ever keep these men in grateful memory.

Having had the privilege of knowing them individually, von Behring unfortunately but slightly, it seemed expedient to write of them at greater length than has been done of the subjects of earlier biographies published in this journal. Recently, in looking through old letters, I found three which I now value greatly as mementoes and which seem to me worthy of publication because of what they contain as records and expressions of the character of the several writers.

**Robert Koch.**

1843-1910.

(Portrait-plate 26 and Facsimile of Letter.)

ROBERT KOCH was born on the 11th of December, 1843, at Clausthal. He was the third child in a family of thirteen, eleven sons and two daughters; two of his brothers died in infancy. The father of this large family was an active and efficient Hanoverian mining official. In 1862, on leaving the Gymnasium,

Robert proceeded to Göttingen to study mathematics, physics and botany, but he soon became a student of medicine and, in his seventh semester, became Assistant at the Pathological Museum under Henle. He took his M.D. in January, 1866. On leaving Göttingen he sojourned for a short time at the Hamburg General Hospital and also near Hanover, after which he established himself, in 1869, in practice at Rakwitz in Posen. He served as a physician during the Franco-Prussian War (1870-1) and in 1872 moved to the little town of Wollstein in the District of Bomst, Polish Prussia, where he became District Physician. Whilst busily engaged in practice, he began to study the subject of anthrax upon which he was destined to throw a flood of light by his researches. His laboratory consisted merely of a curtained-off portion of a large room in which he worked and received his patients. He provided himself with a good microscope and arranged by simple means a photographic room on the premises.

Whilst Koch was working on unaided, the study of microorganisms was being actively pursued by Ferdinand Cohn, Professor of Botany, at Breslau. Cohn's studies had convinced him of the existence of different species of microorganisms and that it was necessary to devise means for their isolation in pure culture. Cohn had discovered certain bacilli which formed spores and actually foretold that the *Bacillus anthracis* would prove to be sporogenous. Cohn was therefore much gratified when he received a letter from Wollstein, dated 22 April, 1876, in which the young physician, Robert Koch, reported that he had made a biological study of the anthrax bacillus and found that it produced spores as Cohn had surmised. The latter immediately invited Koch to visit him and gave Koch the opportunity of demonstrating his specimens and methods to others at the Botanical Institute. Koch's evidence was complete, tracing as it did successively the development of the spores in the bacilli, their liberation, and the sprouting of bacilli from spores. The life-cycle of the bacillus when cultivated in blood serum or aqueous humor was thus demonstrated. Spore-formation was shown to occur in shed anthracic blood and Koch transmitted anthrax by inoculation to mice, rabbits, etc., by the inoculation of anthrax bacilli or their spores. These results threw light into the hitherto obscure etiology of anthrax. Koch's demonstrations greatly impressed his hearers (Cohnheim, Weigert, Traube, and others) and the importance of his discovery made his name known throughout the medical world. His classical researches on anthrax were published in July, 1876, in Cohn's *Beiträge zur Biologie der Pflanzen*; they afforded the first clear demonstration of the causal relationship between a specific microorganism and a specific disease, for it was the first occasion on which a pathogenic organism had been cultivated and the disease reproduced by means of pure cultures. The results obtained by Koch were subsequently confirmed by Pasteur and others.

In 1877 Koch described how coverglass *preparations of bacteria* are made by smearing the substance to be examined upon the glass in a thin layer,

fixing it by the heat of a flame and staining the film by aniline dyes. He showed how the flagella of bacteria could be stained and how microorganisms could be photographed. *Photomicrographs* published by Koch in 1881 have scarcely been surpassed to this day and it must always be remembered that he worked as a pioneer with the simplest of means.

In 1878 he published his researches on the etiology of wound infections and described various improvements in methods including the use of oil-immersion objectives and sub-stage condensers for bacteriological investigation.

In 1880 he was called to the Imperial Health Department, Berlin, where he worked with great diligence and success upon the problems of *disinfection*. His investigations placed the subject upon a scientific basis. He introduced steam-sterilization into practice and taught how this and chemical disinfectants should be applied in accordance with the results of bacteriological tests. The methods laid down by Koch have not undergone any material change because of their fundamental character. Koch was aided in these researches by his pupils Gaffky and Loeffler.

The need of devising *means whereby microorganisms could be readily isolated*, had occupied Koch from the time he first attacked the problem of anthrax. After trying various procedures he bethought himself of adding gelatin, and later agar, to the nutrient fluid medium, thereby discovering a simple manner of overcoming the difficulty. Koch was the first to use solidifying media for the cultivation of microorganisms, and his method has been employed ever since by bacteriologists and others. When Koch demonstrated his method to Pasteur at the International Congress of Medicine held in London in 1881, the great Frenchman exclaimed: "Ah, voilà, c'est un très grand progrès." Up to within a year of his death Koch regarded his discovery of the use of solid media and his methods of bacteriological research as constituting his most valuable contribution to science. There are many who will agree with him having regard to the great results that have followed the employment of Koch's methods by scientific workers throughout the world.

At a memorable meeting of the Berlin Physiological Society, held on 24 March, 1882, Koch announced his discovery of the *Bacillus tuberculosis*. He described a special method for staining the bacillus and of cultivating it upon solidified blood-serum. He demonstrated that tuberculosis could be produced in certain laboratory animals by inoculation with pure cultures of the bacillus. Ehrlich, who was present at the meeting, relates how all who heard Koch speak on that occasion were greatly moved. Ehrlich himself, in 1910, recalls the events of that evening as having afforded him his "greatest scientific experience." Koch spoke in clear and simple language and demonstrated innumerable specimens in a most convincing manner.

To appreciate the full import of Koch's discovery of the tubercle bacillus, we must recognize that he approached the study of the etiology of tuberculosis in a manner contrary to the views of Virchow, which then held the field. Although tuberculosis was recognized as having many forms, Koch regarded

these as all attributable to but one cause, a specific agent that remained to be discovered. He was confirmed in this opinion by experiments of Cohnheim and Salomonsen, wherein tuberculosis of the iris was induced experimentally in rabbits by inoculation, no one at the time having any conception as to the nature of the virus. Koch, as the result of unremitting toil, solved the problem in six months and in such a masterly manner that his name grew famous throughout the world. His discovery will ever stand as a landmark in the history of medicine and the way in which he presented his evidence may well serve as a model for all time.

In 1883 Koch proceeded to Egypt and thence to India to study *cholera*. In Calcutta he confirmed and extended observations begun in Egypt, and was able to announce the discovery of the cholera vibrio as the cause of this dread disease, thereby affording effective means for combating the scourge successfully.

In 1885 Koch was called to the newly-founded *Professorship of Hygiene* at Berlin and, in November, began to lecture at the Hygienic Institute that was established at 36 Klosterstrasse. Students flocked to him from all quarters of the globe and he quickly gathered about him a school of bacteriologists, many of whose members subsequently attained high distinction. Among those associated with him were R. Pfeiffer, M. Kirchner, C. Fraenkel, L. Brieger, G. Gaffky, etc. The Institute was so crowded that when I applied to Koch for admission as a research worker in the autumn of 1886, it was impossible to find a place. Koch received me very amiably but pointed out the crowded heads of men bending over work-benches, seen through the windows across the Court, and advised me to seek more commodious quarters in Carl Flügge's Institute at Göttingen.

An immense amount of work was being turned out of the Institute by Koch and his disciples<sup>1</sup>. After trying in vain to check or ameliorate tuberculosis in animals by chemical agents, Koch made an observation of fundamental importance, namely, that tuberculous guinea-pigs react differently to healthy guinea-pigs when inoculated with living or dead tubercle bacilli. He followed up this clue, reasoning that the tubercle bacillus should give off a soluble substance which would serve as a remedy and means of diagnosis. This substance, which he subsequently found, was prepared as a glycerin extract of pure cultures of the tubercle bacillus. The discovery of the substance, afterwards called *tuberculin*, was announced as a cure for tuberculosis at the International Congress of Medicine, held in Berlin in 1890. Expectations were raised to a high pitch throughout the world owing perhaps to Koch's insufficiently guarded statements as to its efficacy, but chiefly owing to the gross exaggeration of journalists and uncritical medical men. The inevitable result followed in that Koch and his methods became subject to much unwarranted disparagement. The continued use of tuberculin to this day, in the treatment of well-selected cases and in diagnosis, have largely disposed of

<sup>1</sup> See Loeffler's tribute to Koch's stimulating effect on those about him, p. 235.

hasty judgments that were generated by the storm of adverse opinion in which people so commonly follow each other's lead. Subsequently Koch sought to improve upon the original tuberculin, by making a preparation consisting of ground-up tubercle bacilli, but this proved on the whole less efficient than the original tuberculin. The use of tuberculin as a remedial agent constitutes the first attempt at vaccine therapy.

In 1891 Koch, having given up teaching, became the first Director of the newly-founded *Institute for Infective Diseases*. He held this post until 1904, when he was succeeded by Gaffky. Beginning with the year 1896, Koch became engaged in researches which took him abroad, this doubtless being attributable to his disappointment over the reception accorded to his tuberculin as a remedy, coupled with the attitude adopted by society consequent upon his separation from his wife and his second marriage.

In 1896, therefore, at the age of fifty-three, with the best of his life's work accomplished, but brimful of interest in new problems, he left for South Africa, where, at Cape Colony, he proceeded to investigate *rinderpest*. As a method of preventive inoculation he advocated the use of affected animals' bile, a mode of treatment long practised by the natives, and in addition made initial experiments upon the serum therapy of the disease. Thence he proceeded to Bombay as head of the *German Plague Commission*. At this time he was responsible for an edict issued by the German Government forbidding all research work on plague within the precincts of German laboratories. I was then carrying out flea-transmission experiments with plague which, consequent upon this order, had to be suspended. In 1897 he returned to Berlin and the following year found him working on *malaria* in Rome. His researches on malaria were mainly confirmatory of the fundamental work of Ross, and of MacCallum's observations. Anti-malaria measures advocated by him in German East Africa and New Guinea (1899-1900) led to a reduction in malaria-incidence in those countries.

At the International Congress on Tuberculosis held in London in 1901, Koch's pronouncement regarding the *relation between bovine and human tuberculosis* came as a shock to the medical and veterinary professions of the world, running counter as it did to established hygienic measures designed to prevent the infection of man through the agency of tubercular cattle and cows' milk. A measure of justification for Koch's dictum may be found in the circumstance that bovine tuberculosis is relatively speaking infrequently communicated to man, but the attitude of the professions named has nevertheless remained to this day in opposition to Koch's views. This does not militate against Koch's further assertion that man finds in man the chief source of tubercular infection. Koch's attitude on the subject did good service since it led directly to the appointment of a second British Royal Commission for the investigation of the problem.

In 1902 we find Koch working on *Rhodesian or East Coast Fever and Piroplasmosis* (Redwater) of cattle in Africa. In 1903 he celebrated his

sixtieth birthday at Bulawayo. In 1906 he headed the German Expedition sent out to study *Sleeping Sickness* in German East Africa and British Central Africa. Here he employed atoxyl in the treatment of the disease and devised the method of clearing the foreshore of Lake Victoria Nyanza to eradicate *Glossina palpalis* by attacking its breeding grounds.

In 1908 Koch visited his brothers in the United States and, likewise for pleasure, journeyed to Japan, returning thence to Washington to attend a Congress at the instance of his Government. Finally, he returned to Germany to again take up his work on tuberculosis.

For some years prior to his death Koch was occasionally subject to circulatory disturbances, but he nevertheless continued to work uninteruptedly. My late friend Professor Carl Fraenkel, a distinguished pupil of Koch's, recounts how he witnessed Koch's suffering from a heart-attack whilst with him in Japan and how Koch felt his own pulse when he thought himself unobserved. Koch was therefore perfectly aware of his own condition but he worked on persistently. In March, 1910, severer heart-symptoms occurred that were accompanied by dyspnoea and pain in the cardiac region. In April he had a sudden attack of heart weakness with oedema of the lungs from which, however, he rallied sufficiently to travel to Baden Baden comfortably, but eight days after his arrival, nearly at the age of 67, on May 27th, Koch breathed his last peacefully. Three days later, in accordance with his wishes, his remains were cremated at Baden Baden.

Robert Koch was a man characterized by fearlessness, clear and quick insight, good critical judgment, dogged perseverance and great working capacity. His pupils, with whom he stood on an intimate footing, all agreed in stating that he spoke freely with them and was exceptionally amiable and modest, never striving for popularity with the masses, and that his mind was mainly concentrated upon the advancement of science for the benefit of mankind. In his last years, when among intimates, he liked to tell of his varied experiences abroad, and he astonished many by his broad knowledge, especially of botany and zoology. He moreover sought distraction in other sciences, occupying himself for pleasure with such very different subjects as mathematics, physics, chemistry, astronomy, geology, anthropology and ethnology, the last especially during his travels abroad. With strangers, as a rule, he was reserved and a man of few words. Personally I found him most amiable on the occasions when I met him<sup>1</sup>. He was generally acknowledged not to be a graceful speaker.

<sup>1</sup> The last occasion upon which Koch received me in his room at the Institute was in the winter of 1895, when I fell under the spell of his personality. This was not altogether due to our conversation drifting to the subject of immunity and his referring to my researches on the bactericidal properties of blood (*Zeitschr. f. Hygiene*, vol. iv. 1888), of which he spoke as having been "the foundation of the late advances usually spoken of as serum therapy." This recognition, coming from Koch in whose laboratory Behring made his discovery of antitoxic sera, could not but be specially valued by me since Koch knew all the circumstances under which the work had been carried out.

He spoke simply and to the point in a manner that did not fail to impress his hearers.

In Germany Koch's activities were not confined to research and teaching. He was constantly called upon by his Government in an advisory capacity. In 1886, in conjunction with Flügge, he founded the *Zeitschrift für Hygiene*, a journal of high scientific standing which is still appearing.

Many felt that the weight of Koch's authority in his domain was at times too great, especially in its influence on Government, and, unless Koch expressed a favourable opinion of a discovery, it was liable to be received with doubt by German men of science. Moreover, when Koch or members of his school had been given the opportunity of confirming the work of others, there was a decided tendency to arrogate to themselves undue credit in discovery. This resulted in ill-feeling that was none the less bitter because it did not always find its way into print. Men feared to stand up against Koch because they felt his influence, if directed against them, might injure them in their career or lead to the loss of a coveted post. Under the circumstances, Koch was in a position to push others aside and on occasion he did so. Thus, to my knowledge, when an obscure but observing young veterinarian in German East Africa had found *Piroplasma bigeminum* in cattle suffering from redwater and had shown the parasites to Koch, we only heard of Koch's work thereon afterwards. When Metchnikoff brought malaria blood-films from Russia in 1887, and demonstrated these to Koch, he was treated, as he told me himself, with scant courtesy, for Koch apparently still disbelieved in the existence of the malaria parasites that Laveran had discovered in 1880; at any rate Koch denied that Metchnikoff's slides showed malaria parasites. The latter had, however, demonstrated his excellent preparations to Professor Flügge and to me some days previously in Breslau and we had seen the parasites. This experience certainly hastened Metchnikoff's journey on to Paris. Furthermore, when Grassi, Bignami and Bastianelli in Rome, stimulated and directly guided by the epoch-making discoveries of Ronald Ross on malaria, confirmed and extended the latter's work, the antagonistic attitude adopted by Koch was extreme. It was therefore generally held in Berlin that the work of the Italian observers was worthless, and it was not until I demonstrated some of Grassi's specimens in Berlin, after having gone to Rome (March 1st, 1899) to fetch them, that a measure of credence was given by some authorities in Germany to the reported results of the Italian researches<sup>1</sup>.

<sup>1</sup> It must be assumed that Koch did not see any of the preparations made by Grassi and his colleagues, for so late as 10th February, 1901, close on two years after I visited Grassi, Koch wrote to Ross (vide *Memoirs* by Ronald Ross, London, 1923, p. 409) of Grassi's work: "His statements regarding the development of the malaria parasites in the mosquito's body, if really observed by him as described (which I do not believe), are but a confirmation of your discoveries. His illustrations are direct copies of yours" (my translation). Whilst agreeing that Grassi's claims to original discovery deserve some of the criticism they have received, it is but fair to separate the good from the bad and to give him and his colleagues their due. When in Rome, I compared the Italian authors' figures with their specimens and found them to agree. I still possess some of these specimens and it cannot be asserted that they are the products of Grassi's imagination.

Although it is unpleasant to dwell on this aspect of Koch's character I have felt it incumbent upon myself to do so with a view to giving a true picture of the man, not as he might have been but as he was. The instances I have cited might be multiplied, but they will suffice to show that, great as he was, Koch had his weaknesses. I presume that constant appeals to him for his opinion may have adversely affected his judgment on some matters, in which case there are obvious disadvantages in being too great an authority in the eyes of one's fellow-men.

To recapitulate briefly, Koch's work was fundamental in respect to the methods to be pursued in bacteriological investigation; we have to thank him still for many every-day methods that are employed in laboratories, hospitals, preventive medicine and public health. He threw light upon the etiology of anthrax, discovered the cause of tuberculosis and cholera, thereby placing in our hands the means of diagnosis and indicating how these diseases may be combated. By a careful study of the processes of water-filtration he laid down principles for the prevention of water-borne diseases like cholera and typhoid. His thorough and methodical work upon the theory and practice of disinfection by heat and by chemicals still serves us as a guide. His contributions to tropical medicine and parasitology, especially in relation to East Coast Fever in cattle, Malaria, and Sleeping Sickness were important.

Research upon Immunity, which was pursued by purely empirical methods before the advent of Pasteur, attained a great impetus in bacteriological laboratories through the influence of Koch and his methods. Bacteriotherapy, now so much in vogue largely through the efforts of Almroth Wright, may be regarded as having had its birth in the discovery of Koch's tuberculin as a remedial agent. It was in Koch's laboratory that Behring discovered the first antitoxin, and that Pfeiffer discovered bacteriolsins. It was Koch who first advocated the systematic use of quinine in combating malaria, for he conceived that this disease could be eradicated by discovering the infected persons in a community and subjecting them to radical treatment, thereby ridding

When two observers illustrate what amounts to the same thing, it is to be expected that their figures will closely correspond. Ross's figures were those drawn by a pioneer working single-handed under great difficulties whilst seeking out fundamentals, those of the Italians were the products of a European laboratory with a technically-trained staff. By good sections, excellent staining technique and an artist's help, this staff naturally produced specimens and illustrations which greatly surpassed those of Ross and consequently appealed more strongly to zoologists, though they established no principles other than those laid down or indicated by the work of Ross.

It is clear that full credit must be given to Grassi and his colleagues for having been the first to demonstrate that the human malaria parasites have a cycle of development in *Anopheles* corresponding exactly to that demonstrated by Ross for *Proteosoma* in *Culex*. On the other hand there can be no question but that Ross observed the early stages of the development of one species of human malaria parasite (*praecox*) in *Anopheles*. Unfortunately, for reasons which are fully explained in his *Memoirs*, Ross was unable to do more than to predict that the immature forms ("pigmented cells," 1897) observed by him in *Anopheles* would complete their development as in *Proteosoma*. For a full discussion of this subject, see Nuttall (1902), "On the Question of Priority with Regard to certain Discoveries upon the  $\text{\textit{A}}\text{\textit{etiology}}$  of Malarial Diseases," *Quarterly Journal of Microscopical Science*, n.s. vol. XLIV. pp. 429-441.

them of parasites and rendering them no longer capable of infecting the anopheline vectors. He moreover introduced atoxyl in the treatment of Sleeping Sickness in Africa.

The value of the services Koch rendered to his country and mankind throughout the world led to his having the title of Excellency conferred upon him by the German Emperor in 1907, but he was not granted the patent of nobility, doubtless owing to his domestic relations. He was awarded the Nobel Prize in 1905, and was the recipient of many honours from learned societies and universities, besides decorations of which may be mentioned the rare *Ordre pour le Mérite* conferred upon him by his Sovereign. The Institut für Infektionskrankheiten "Robert Koch" remains as a visible memorial of him. Koch, through the magnitude of his services to mankind, will ever be kept in grateful memory. In the annals of medicine his name should be enrolled with the immortals.

The accompanying portrait of Robert Koch dates from about the year 1907, some three years before his death.

*See facsimile<sup>1</sup> of a letter by Robert Koch to G. H. F. Nuttall on opposite page.*

*Translation:*

The thought that mosquitoes play an important part, possibly the whole part in the etiology of malaria, came to me during my first sojourn in India in 1883-4, when for the first time I learnt to know the conditions: under which tropical malaria flourishes and highly malarious regions; since then I have always expressed myself in this sense, especially in my lectures and courses. Naturally, I have not referred to this until recently, but R. Pfeiffer mentions it in his *Beiträge zur Protozoenforschung*, Berlin, 1892, p. 22.

REFERENCES.

In writing the foregoing biography I have made free use of publications that were kindly sent to me in reprint form in 1910, shortly after their appearance, by Professors Carl Fraenkel (*München. med. Wochenschr.* p. 1345), P. Uhlenhuth (*Med. Klinik*, No. 24), G. Gaffky (Gedächtnisrede in *Deutsche med. Wochenschr.* No. 50), and subsequently by Dr W. W. Ford (*Johns Hopkins Hosp. Bulletin*, 1911, vol. xxii. p. 415, giving list of chief publications) and Prof. W. Kolle (*Med. Klinik*, 1913, Nos. 51-2). See also C. J. Martin (*Brit. Med. Journ.* 1910, vol. i. p. 1386, and editorial on p. 1384) and P. Ehrlich (*Zeitschr. f. Immunitätsforsch. u. exper. Therap.* 1910, Orig., vol. vi. part 1). W. Becher (1891), *Robert Koch, Eine biographische Studie*, may be consulted, likewise Koch's earlier publications issued (1886) in English translation by The New Sydenham Society.

<sup>1</sup> Reduction by 1/5.



ROBERT KOCH

1843—1910



Berlin N. W. Charlottenstr. 1.  
J. 14. Nov. 1898.

Grußgruß der Frau Bellay!

Nur gestalte, daß die Begrüßungen in der Übersetzung  
zur Malarien nicht verschwunden, wenigstens nicht  
in einzigen Dellen geblieben, dann wird bei meinem  
ersten Aufenthalte in Jodus 1883/84, als ich von  
einem Nachtheil der Begrüßungen zuvor durch die  
Englische Malarien geschafft und gegen die Malarien  
verwendeten Namen hörte. Der Name führt  
sich nur in seinen Namen, verantwortlich  
für in seinem Versteigen und Werken und  
Gesetzgebungen. Bellay veröffentlich führt ist kein ver-  
steigern Wörter nicht, aber R. Koch

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veröffentlicht in seinem: Eintragen zur  
Parasitenforschung Berlin 1892. p. 22.

Zufriedenstellend

R. Koch

## Paul Ehrlich.

1854-1915.

(Portrait-plate 27.)

PAUL EHRLICH was born on the 14th of March, 1854, at Strehlen in Silesia. After leaving the Maria-Magdalena Gymnasium in Breslau, he went as a University student to Breslau, Strassburg, Freiburg and Leipzig successively. He took his M.D. in Strassburg in 1878. He was influenced by the teachings of Waldeyer, Heidenhain and Cohnheim and at an early date showed his aptitude for research. Whilst still a student he devoted himself to the study of the *histology of the blood*. In Breslau (1877), before he became professionally qualified, he was struck by the existence of a chemical affinity between certain organs and chemical poisons as instanced in the case of lead; this served as a basis upon which he subsequently built up his theory of *selective anchoring* which was grounded on the belief of the existence of chemical affinity between certain tissue cells and a particular poison. This conception dominated his viewpoint to the end of his life. His work on blood led to his becoming interested in *aniline dyes* this interest being especially stimulated through his cordial relations with his cousin Karl Weigert.

In 1878-85 he was stationed at the Charité Hospital in Berlin as assistant under Frerichs. Here he worked out methods of blood diagnosis and of colour analysis, upon the diazo-reaction (1883), on the affinity possessed by methylene-blue for living nervous tissue-elements, upon specific staining reactions of the tubercle bacillus and its acid-fastness (1882). In 1885-7 he was assistant to Gerhardt and during this period he published his monograph, *Das Sauerstoffbedürfniss des Organismus* (1885), which embodied the results of his researches. This contribution already outlines the principles upon which he based his famous "side-chain theory" that he evolved many years later; this work still affords stimulating reading. In 1888 Ehrlich suffered from what appeared to be but an obstinate catarrh, but on examining his sputum he found it to contain tubercle bacilli. He therefore went to Egypt, underwent a course of treatment with Koch's tuberculin, and, having recovered from his symptoms, returned to Berlin to pursue his researches. He became Privatdocent in 1889, and in 1890 received the title of Professor also being made Mitarbeiter at the Institute for Infective Diseases. He at first worked on tuberculosis in association with Koch and afterwards alone on the subject of *immunity in relation to vegetable poisons* (ricin, abrin and robin), finding that he could immunize animals against these poisons, corresponding antitoxins being formed in their blood; these antitoxins, being eliminated in the milk of immunized animals, served to immunize their offspring.

Ehrlich now attacked the fundamental problems of immunity and *serum therapy*. Guided by his experience in immunizing animals against the poisons of higher plants, above mentioned, and having regard to Behring's discovery of the antitoxins for bacterial poisons, he worked methodically upon the

production of *diphtheria antitoxin*, thereby furnishing a curative serum that could be used in medical practice. Considered scientifically, this was of subsidiary importance. The chief credit that lay in Ehrlich's work at this period was his introduction of *quantitative methods* into work on immunity problems, in his distinguishing *active* from *passive immunity* (he established this terminology), and applying his experience as a chemist to the problem of evolving methods whereby the potency of toxins and antitoxins could be tested. This work of Ehrlich's (1896) gave us the methods that are being used to the present day.

In 1896 he was placed at the head of the newly-founded *Institute for Serum Testing and Serum Research at Steglitz*, near Berlin. It was a joy to him to be in a laboratory of his own where he could work on independently. To those of us who knew the circumstances under which he laboured at Koch's Institute it was common knowledge that his freedom in carrying on research was being interfered with. Soon after he had established himself in his new quarters, I sought him there and found him in the company of L. Brieger. It was touching to see his delight in at last finding himself complete master of his own actions. His work at Steglitz, pursued with enormous energy, led to the exposition of his *side-chain theory*, according to which the effect of a toxin on a particular organ is due to the cells of that organ containing substances ("receptors") having a special affinity for the toxin. Owing to this affinity the toxin becomes fixed in the particular organ. The antitoxins are merely receptors, thrown off into the blood, which, through their toxin-binding group hinder the access of toxin to the living cell, thereby protecting the cell against injury. This theory, as Ehrlich showed, also applied to problems of cell nutrition. Ehrlich's theory has exerted a profound influence upon research on these problems and it was the dominant conception that guided his work for years.

In 1899 Ehrlich became Director of the newly-founded *Institute for Experimental Therapy* at Frankfurt a.M., and commenced to publish his important researches on *haemolysins* and their mode of action. In haemolysis, according to his theory, amboceptors are cast off by the cells into the blood and serve as factors when coupled with the fermentative complement. This work on haemolysis led directly to Wassermann's discovery of the method of sero-diagnosis in syphilis, as Wassermann himself (1915, p. 1105) gratefully acknowledges. In 1904 he published his *Gesammelte Arbeiten zur Immunitätsforschung*, which appeared in English translation in 1906. Ehrlich, moreover, conducted important researches on *malignant tumours*, first producing carcinoma in 100 per cent. of his experimentally-inoculated mice so as to proceed from a secure basis of constant production of the malignant growth. His studies related to experimental immunity to mouse carcinoma and to transition forms between carcinoma and sarcoma.

Soon after Ehrlich had become established in Frankfurt, Frau Francisca Speyer became a benefactor to medical science by founding the *Georg Speyer*

*Haus* in memory of her husband. This building was erected beside the Institute for Serum Therapy and it was placed at Ehrlich's disposal, thereby facilitating the remarkable researches which occupied him to the end of his life. This, and the naming of a street after him ("Paul Ehrlich Strasse") by the city of Frankfurt attest to the esteem in which he was held by his fellow-citizens.

Ehrlich now plunged into a line of research that was especially congenial to him, namely *systematic investigations on chemo-therapy*. Many years before he had recommended methylene-blue for the treatment of malaria because of its destructive effect on the parasites. He began by attacking *trypanosomiasis* and discovered *trypanred* to be a remedy. He discovered that the trypanosomes in treated animals acquired the power to resist the trypanocidal effect of drugs. He cleared up the chemical constitution of *atoxyl* and made way for systematic work on organic arsenic compounds destined for chemo-therapeutic use. He and his collaborators produced *arsacetin* and *arsenophenylglycin*, which were both trypanocidal, but they were found to exert an unfavourable effect upon the infected host. He next made the brilliant discovery of the *salvarsan* group, including the celebrated preparation "606" which has proved so astonishingly efficient in the treatment of spirochaetal infections and which has since been used throughout the world for the treatment and cure of syphilis. This last discovery was a veritable triumph for Ehrlich, a crowning achievement following upon an enormous amount of systematic labour carried on over a period of many years. Salvarsan has proved efficient in the treatment of relapsing fever, and *Framboesia tropica*. In the latter instance it has proved so effective that many hospitals could be closed because they were no longer needed for the reception of cases. Moreover, during the war, salvarsan proved trustworthy in the treatment of equine influenza (pink-eye), and even in the treatment of bacterial infections (swine erysipelas, anthrax and glanders), thereby exploding the dogma that pathogenic bacteria in an animal's body cannot be destroyed by drugs. This discovery makes us hopeful regarding what we may expect from future research similar to that launched by the genius of Ehrlich. Finally, continuing his researches, Ehrlich discovered *neosalvarsan*, and, by introducing heavy metals, especially copper, into his salvarsan-complex, he greatly increased the trypanocidal action of this remedy.

During the latter years of his life Ehrlich suffered from progressive arteriosclerosis and therewith connected renal trouble and diabetes. All who knew him, who gave the matter a thought, were convinced that he would not live long. He burnt the candle at both ends, working mind and body to the uttermost limit, year in and year out. He lived in a veritable turmoil of work until close on the end, when he went for reasons of seriously failing health to Bad Homburg, where he died on the 19th of August, 1915. Emil von Behring delivered the oration at Ehrlich's grave on the 23rd.

Ehrlich was an idealist who, regardless of himself, devoted his whole working life to discovering means for alleviating and preventing human

suffering. The Great War came to him as a terrible catastrophe, for, with its advent, he saw all his ideals crumble into dust. There is no question but that the war hastened his death. He had many friends. The loss of his stimulating personality has been felt by all who came within the radius of his genius.

The magnitude of Ehrlich's work can best be gleaned from his *Festschrift*, issued to commemorate his 60th birthday. This work contains a biography, a complete survey of his many-sided scientific activities and that of his associates, a complete bibliography of his published work, besides sections written by many distinguished authors and pupils of the master. A long list of the many papers published by him and his pupils in the *Deutsche medicinische Wochenschrift*, between the years 1881 and 1914, will be found in that journal (1915, p. 1136).

Contrary to Koch, who on the whole avoided scientific controversy, Ehrlich on occasion spoke out sharply. The transparent honesty of the man and his enthusiasm for his work, coupled with the ingenuity with which he built up line after line of defence to guard his theoretical conceptions against aggression, could not but evoke sympathy and admiration even in the ranks of his opponents. In this respect he often reminded me of Metchnikoff in the days when the latter sought to defend his phagocyte theory against attack; he too was deeply sincere and enthusiastic but, because of his highly-sensitive nature, he suffered more in the conflicts upon which he entered. Whatever the antagonistic opinions were or ultimately will be regarding the theoretical conceptions advanced by Ehrlich and by Metchnikoff, they also have this in common that they stimulated thought and the search after the truth throughout the world among workers on immunity. This in itself was a great achievement.

The accompanying portrait of Ehrlich is reproduced from one he gave me in the year 1902; it is an excellent likeness since it conveys a true impression of his quick nervous temperament, whilst in his hands he, in characteristic fashion, holds one of those excellent Havana cigars from which he was rarely parted.

\* \*

The following characteristic letter from Ehrlich is here added because of its exceptional interest. The book referred to in the first paragraph is *Blood Immunity and Blood Relationship*, xii+404 pp. (Cambridge: University Press), published by me in 1904, of which the dedication reads: "This volume is dedicated to *Paul Ehrlich* and *Élie Metchnikoff*, whose genius and influence have greatly advanced and stimulated the search after truth amid the complex problems of immunity." The Nobel Prize for Medicine, to which they were equally entitled, was divided between them in 1908!

GEH. MED. RATH PROF. DR. P. EHRLICH.

WESTENDSTRASSE 62,  
FRANKFURT A/M., 29. Februar, 1904.

Hochverehrter und lieber Freund!

Eben im Begriff, nach Amerika abzufahren, habe ich Ihr Buch erhalten, dessen Widmung mich ausserordentlich erfreut hat. Ich danke Ihnen herzlich für diesen Beweis Ihrer treuen Gesinnung und Anhängerschaft, der mich umso mehr erfreut hat, als ja gerade Sie durch Ihre so erfolgreiche und reiche Arbeit zu einem objektiven Urteil vor so vielen andern befähigt sind.

Ebenso lieb war es mir, dass gleichzeitig das Buch auch Metschnikoff gewidmet ist, zu dem ich, wie Sie ja wissen, auch persönlich in den besten Beziehungen stehe und dessen Leistungen ich ebenso hoch schätze wie Sie. Dass wir in manchen Punkten anderer Ansicht sind, ändert an meiner Verehrung und Liebe für diesen Mann garnichts.

Ich bin jetzt, nachdem Gruber wohl endlich mundtot gemacht<sup>1</sup> sein wird (?) in heftigem Streit mit Arrhenius, der mich eigentlich zu schlecht behandelt hat. Die neueren Arbeiten des Instituts haben mir gezeigt, dass seine unitarischen Anschaulungen ganz irrig sind und ich mit meiner eine Pluralität verschiedener Gifte voraussetzende Ansicht doch recht behalte. Ich weiss übrigens auch, dass hervorragende physikalische Chemiker die Beweisführung von Arrhenius auch vom rein theoretischen Standpunkt aus für durchaus nicht beweisend halten.

Mit nochmaligem herzlichem Dank,  
Ihr freundschaftlich ergebener  
(facsimile of signature)

HERRN PROFESSOR DR. NUTTALL,  
UNIVERSITY OF CAMBRIDGE,  
CAMBRIDGE.

The translation of this letter (typewritten, as were all the others received by me) reads as follows:

HIGHLY HONOURED AND DEAR FRIEND!

Just when about to start for America, I receive your book, the dedication of which has given me extraordinary pleasure. I thank you heartily for this proof of your faithful sentiment and attachment which pleases me all the more since you especially, through your so successful and abundant work, are so much more capable than many others to form an objective judgment.

<sup>1</sup> "Mundtot gemacht," as an expression has a charm of its own, meaning literally "made mouth-dead."



PAUL EHRLICH

1854—1915



Equally gratifying to me is it that the book is also dedicated to Metchnikoff, to whom, as you know, I also stand in the best relations and whose contributions I esteem as highly as do you. That we differ in some points does not affect in the slightest my respect and affection for this man.

Now that Gruber has presumably been finally silenced (?), I am in violent conflict with Arrhenius, who really has treated me too badly. The new papers from the Institute have shown me that his unitarian views are entirely wrong and that I with my opinion which assumes the plurality of different poisons am nevertheless right. I know, moreover, that leading physical chemists also regard the evidence produced by Arrhenius as by no means convincing from a purely theoretical point of view.

Again with hearty thanks,  
Yours, etc.

#### REFERENCES.

In writing the foregoing biography I have borrowed freely from the admirable publication by Professor A. von Wassermann (*Deutsche med. Wochenschr.* 1915, pp. 1103-6). See also P. H. Römer (*ibid.* 1914, pp. 521-4, with portraits of Ehrlich and Behring), "J. S." (*ibid.* 1915, p. 1046), and Paul Ehrlich. *Eine Darstellung seines wissenschaftlichen Wirkens* Festschrift zum 60. Geburtstage des Forschers. 668 pp., portrait. Jena: G. Fischer, 1914.

#### Emil von Behring.

1854-1917.

(Portrait-plate 28.)

EMIL VON BEHRING was born on the 15th of March, 1854 (a day after Paul Ehrlich), at Hansdorf, near Deutsch-Eylau in East Prussia, where he received his early education at the Gymnasium of Hohenstein. He studied at the Army Medical School in Berlin, graduated M.D. in 1878, and passed his State examination in 1880. He then served in the army in Silesia, Posen, and finally Bonn, whither he went in 1887.

Happily for science, as subsequent events proved, Behring had occasion to dress the wounds of soldiers with *iodoform*, a remedy then commonly employed in the treatment of wounds. Iodoform then, and to my recollection for many years afterwards, scented the air of hospitals, German students' duelling grounds and the restaurants and beer gardens in which students congregated with their faces bound up with iodoform dressings. Behring could therefore scarcely escape from the ever-reminding odour of this efficient but disagreeable substance. The efficacy of iodoform was attributed to its directly antiseptic properties until Behring took up the study of its mode of action. He was the first to prove that iodoform modifies the products of putrefaction. In 1882, whilst not denying its bactericidal properties, he laid stress upon the chemical reactions that take place between iodoform and bacterial products. Subsequently he proved that iodoform acts by virtue of its breaking up in contact with the tissues and bacteria, whereby *iodine* is liberated. He argued that the curative action of iodine must depend upon its modifying bacterial products.

At that time Brieger's researches upon ptomaines led many to suppose that ptomaines constituted the essentially toxic products elaborated by bacteria. Behring therefore tested iodoform as against Brieger's cadaverine. He found that iodine lessened the toxicity of cadaverine. Therefore he concluded that remedies for bacterial diseases must be sought among substances capable of neutralizing the poisons of microbes. The conception of *antitoxins*, from now on, floated before his mind.

In 1888 he was ordered to Berlin, but prior to his departure, whilst working in the Pharmacological Laboratory at Bonn, he completed his first studies upon the serum of white rats, which were then regarded as uniformly immune to anthrax. These studies, published in 1888, were directly stimulated by the researches of Fodor (1886), but especially of Nuttall on the *bactericidal properties of serum* (vide Nuttall, *Zeitschr. f. Hygiene*, 1888, iv. pp. 353-94). Behring believed that the bactericidal property of the rats' serum was due to its alkalinity, and consequently that the immunity of these animals was due to the chemical constitution of their serum. Subsequently, however, Behring and Nissen found that the serum of guinea-pigs immunized against *Vibrio metchnikovi* possessed great bactericidal power. It was, however, found that an animal yielding a bactericidal serum was not immune to anthrax and that various pathogenic organisms grew well in corresponding immune sera. Therefore the bactericidal properties of serum did not offer a satisfactory explanation of immunity. Behring now bethought himself of his experiments upon the antagonistic effect of iodine on ptomaines and asked himself if immunity did not perchance depend upon the formation in the animal body of an antitoxin for the poison elaborated by the pathogenic microorganism.

At this stage Behring was aided by the discoveries of others. In 1888-90 Roux and Yersin discovered that unheated cultures of the *Bacillus diphtheriae* contained a toxin and soon after K. Faber (1890) and Kitasato discovered that *Bacillus tetani* likewise liberated a toxin. The impulse given by the work of Roux and Yersin was most important in pointing a way to the solution of the problem; they proved, moreover, that the toxin of the diphtheria bacillus was entirely responsible for the pathogenic effects of this microorganism. It was promptly recognized that these bacterial toxins were of an entirely different nature to the ptomaines, of unknown composition and infinitely more potent; nevertheless the discovery of these toxins helped to clear Behring's conceptions regarding the nature of acquired immunity, especially when, in 1890, he and Carl Fraenkel found, simultaneously, that animals could be rendered immune against diphtheria toxin.

Before proceeding I would mention here that Behring became Robert Koch's assistant at the Hygienic Institute, Berlin, in 1889, and that subsequently he worked under Koch at the Institute for Infective Diseases. In 1893 the title of Professor was conferred upon him.

After finding that the serum of guinea-pigs that had been rendered immune to diphtheria bacilli or their toxins, did not kill the bacilli, Behring, in the

summer of 1890, was led to test if the serum had any effect on the toxin of the diphtheria bacillus, and behold it neutralized the toxin! In a paper published on the 4th of December, 1890, was made the important announcement of the discovery of the antitoxins for diphtheria and tetanus (see Behring and Kitasato, *Deutsche med. Wochenschr.* XVI. 1113). Little time had been lost. The initial discovery with diphtheria had been made in the summer, that with tetanus in the autumn. In the latter case Behring worked with Kitasato, the experimental animals being mice. In 1890-93 Behring and Wernicke succeeded in curing small laboratory animals and immunized sheep and dogs against diphtheria toxin; even the sensitive mouse could be cured in the early stages of tetanus infection. By Christmas, 1891, it was possible to make the first trials with diphtheria antitoxin on man, and by January, 1892, the fundamental principles relating to the methods of producing curative sera, their dosage, testing and application had been determined. These developments were influenced by the work of Ehrlich. In 1892-3 the immunization of horses was begun, on the principles established by Ehrlich for the vegetable poisons abrin, ricin and rubin, and in 1894 diphtheria antitoxin could finally be issued to practitioners of medicine for employment in the treatment of diphtheria in man.

Behring's discoveries regarding the value of diphtheria antitoxin were brilliantly confirmed by Émile Roux in 1894. None of us who listened to Roux's masterly exposition that year, at the International Congress of Hygiene and Demography, Budapest, will forget the deep impression engendered by his pronouncement and the enthusiasm it evoked.

After temporarily filling the Chair of Hygiene at Halle in 1894, Behring, in 1895, became Professor of Hygiene and Director of the Hygienic Institute in the University of Marburg. Here he developed extensive laboratories which finally became known as the "Behringwerk," these being destined to forward the application of scientific discoveries in practice. During the Great War large quantities of tetanus antitoxin were issued from the Behringwerk for use in the army. It was not until this war that tetanus antitoxin was used extensively by the contending nations, although the certainty was clearly established years before that it would prove of enormous value. Curiously enough the nations were caught napping in this respect when the war broke out, in consequence of which many valuable soldiers' lives were lost through what should have been avoidable tetanus. In an obituary notice of Edmond Nocard (*Journ. of Hygiene*, 1903, vol. III. p. 519) I wrote of the latter: "His studies on the preventive use of anti-tetanic serum in horses were likewise of great practical and economic importance, and should have a bearing upon the prevention of tetanus in man." Then, and for years after, I urged upon all suitable occasions the employment of the antitoxin on man and occasionally succeeded in having it employed. The matter was so obvious to anyone giving it a thought that it seems incredible for a war to have been required to drive the lesson home. Wernicke, a former collaborator of

Behring's, writing in 1917, actually states that the proof of the great value of tetanus antitoxin in the prevention of tetanus in man was first established through experience gained in the late war.

In tracing the development of Behring's work, we see that he commenced by studying natural immunity and thence proceeded to investigate the causes leading up to the establishment of acquired immunity. He was then able to produce passive immunity, but he was not content with this, he sought to establish the more durable condition of active immunity. His work during the last years of his life concerned itself largely with efforts to establish active immunity against diphtheria in children; he sought to attain this by the administration to them of diphtheria-toxin together with antitoxin. He moreover did an enormous amount of work on tuberculosis which through no fault of his was not crowned with all the success it deserved.

For his discovery of antitoxin Behring was awarded the prize of the Académie de Médecine and Institut de France (1895) and of the Senckenberg Institute of Frankfurt, and he received well-merited recognition from other sources in the form of decorations and of diplomas of universities and learned societies. In 1901 he received the patent of nobility, which entitled him to the prefix *von* before his name, and in the same year he was awarded the Nobel prize. In 1903 he became Privy Councillor and had the title of Excellency conferred upon him by the German Emperor.

After years of illness he died on the 31st of March, 1917, at the age of 63, the cause of death being acute pneumonia. He was buried on the 4th of April in a mausoleum he had himself erected in Marburg.

The accompanying portrait of Behring is reproduced from a photograph obtained from him in 1907 through the kind intermediation of my friend the late Professor Loeffler. It is an excellent likeness.

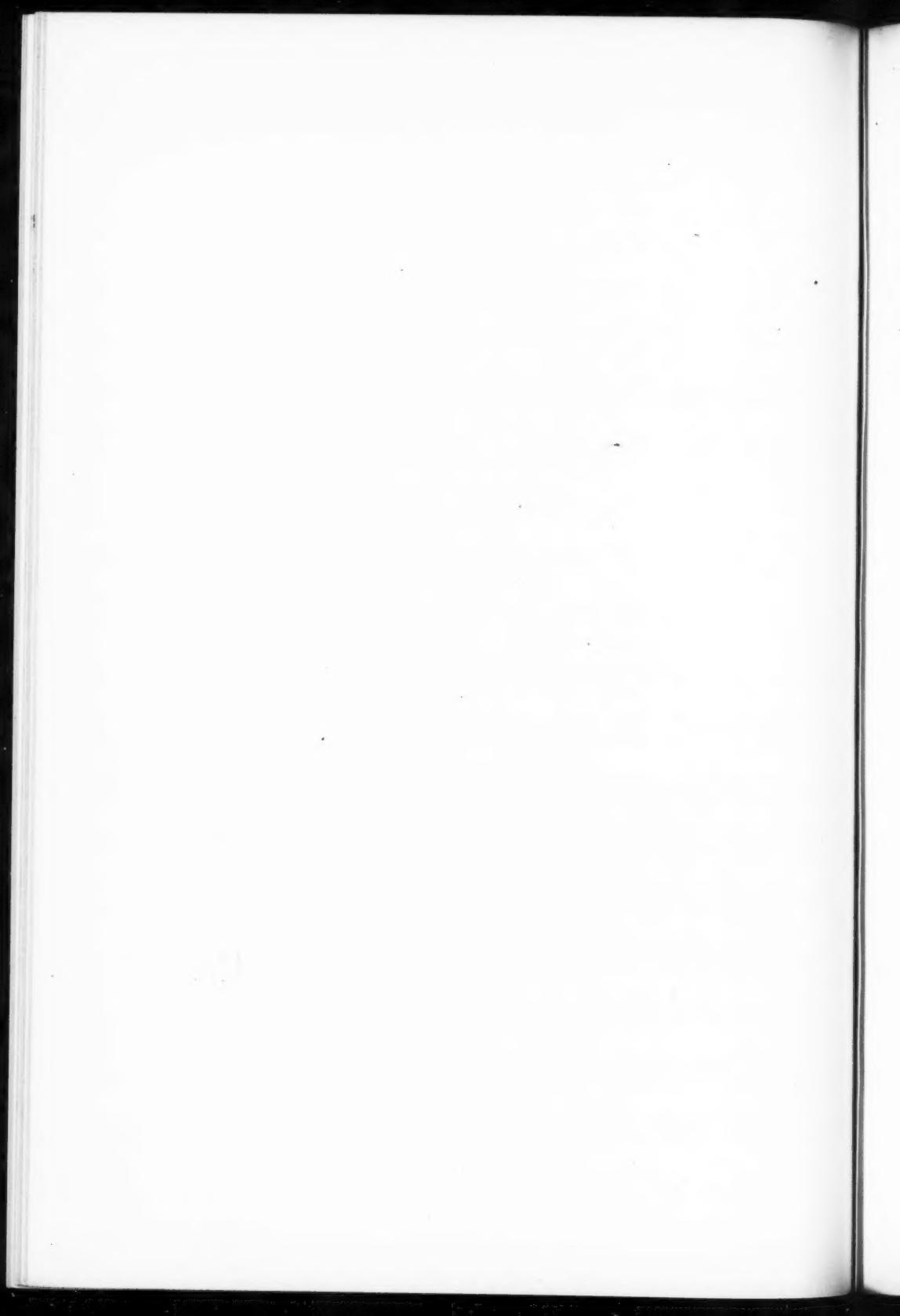
\* \*

Rarely in the history of scientific discovery have the results of laboratory researches been followed so rapidly by their practical application, and few indeed are the workers in the domain of medical science who have in their life-time seen comparable benefits accrue to mankind as a direct consequence of their labours. The discovery of diphtheria antitoxin has saved many thousands of lives throughout the world and robbed diphtheria to a great extent of its terrors, as everyone knows who recalls the tragedies of pre-antitoxin days. Not only was the discovery of immense and immediate practical importance but it stimulated scientific research on immunity to an extraordinary degree and these researches have borne, are bearing, and will bear much fruit. The discovery of serum-therapy by Behring is one of the greatest recorded in the history of medicine since it ranks alongside of the discovery of vaccination by Jenner and of antiseptic surgery by Lister.



EMIL VON BEHRING

1854—1917



## REFERENCES.

For a masterly exposition of the progress of scientific research leading up to and following the discovery of antitoxins by Behring, see Chapter I, written by F. Loeffler, in *The Bacteriology of Diphtheria*, edited by Nuttall and Graham-Smith, xx + 718 pp., which appeared in 1908 (Cambridge: University Press). This work contains a full bibliography of Behring's work and that of others dealing with diphtheria, and, in the biographical notice of Behring, given on p. xx, will be found a list of his more important publications. Behring was a much more luminous writer than Koch. Our portrait of Behring and that of Loeffler which follows, are printed from the same blocks that were used for the portraits that appeared in the above-mentioned work. See also the tribute ("Huldigung") by P. H. Römer, published to commemorate the 60th Anniversaries of Ehrlich and Behring in March, 1914 (*Deutsche med. Wochenschr.* pp. 521-4, with portraits); the highly appreciative tribute by É. Roux and É. Metchnikoff (*ibid.* Sonderbeilage No. 11); the obituary notices which appeared in 1917, from the pens of E. Wernicke (*ibid.* pp. 662-4, with list of publications in that journal during the years 1882-1915), H. Kossel (*Berlin. klin. Wochenschr.* p. 471), M. Mathes (*München. med. Wochenschr.* p. 585), M. von Gruber (*ibid.* pp. 1235-9).

## Friedrich Loeffler.

1852-1915.

(Portrait-plate 29, and Facsimile of Letter.)

FRIEDRICH AUGUST JOHANNES LOEFFLER was born on the 24th of June, 1852, at Frankfurt a.O. His father, Gottfried Friedrich Franz Loeffler, was a man of distinction. He did much to raise the status of medical officers in the army, held the position of Sub-Director of the Kaiser-Wilhelm's Akademie für das militärärztliche Bildungswesen, Berlin, attained the rank of Generalarzt with the title of Professor, had the Iron Cross of the 1st Class conferred upon him and, posthumously, a marble bust erected to his memory in the Academy. Friedrich received his early education at Marburg, in the Gymnasium zum grauen Kloster, and in Berlin, at the Collège Royal Français. He studied medicine in Würzburg and subsequently at Berlin, and served as a hospital assistant in the Franco-Prussian war. He took his M.D. in 1874, passed his State Examination in 1875, and was subsequently stationed as a military surgeon in Hanover and Potsdam, where he practised medicine. In 1879 he was ordered to the Imperial Health Department together with Hueppe and Gaffky, and during 1880-84 worked with Robert Koch. In 1886 he became Privatdocent in Hygiene at the University of Berlin, and in 1888 received two calls: to fill the Chairs of Hygiene in Giessen and in Greifswald. He chose Greifswald.

During four years (1903-7) he served as Rector of the University of Greifswald. In 1905 he was raised to the rank of Generalarzt in the Army Medical Corps, and in 1913 succeeded Gaffky as Director of the Institut für Infektionskrankheiten "Robert Koch," in Berlin. During the Great War he served as Generalarzt and hygienist; it was too great a strain for a man of his years, although outwardly he appeared as vigorous as ever. He began to fail

in December, 1914, and was compelled to return in the following January to his home. After much suffering and undergoing an operation which could not alleviate his condition, he died on the 9th of April, 1915. Gaffky relates that Loeffler's mind was occupied with thoughts of scientific problems to the end—even in his delirium. Friedrich Loeffler lies buried in Greifswald.

The importance of Loeffler's bacteriological work, which covered a wide range, may be judged from the following brief summary. In 1882 he (with Schütz) discovered the cause of glanders (*Bacillus mallei*) and described its biological characters. In the same year he discovered the *Bacillus diphtheriae*, described its biology, showed how local is its distribution in the body and indicated that its far-reaching effects were attributable to a diffusible poison, that the procedure to be adopted in treating the disease was to destroy the organisms locally by suitable antiseptics and by seeking means of neutralizing the toxin. This served as a sign-post to Behring in his work that resulted in the discovery of diphtheria antitoxin. Loeffler also discovered the existence of the non-pathogenic *pseudo-diphtheria* bacilli, and the organisms that give rise to diphtheria-like affections in pigeons and calves (1884). In 1885 he discovered the cause of swine erysipelas (*Bacillus erysipelatis suis*), and swine plague (*B. suispticus*), and, in 1891, *B. typhi murium*. The last, which caused mortality among mice at the Institute in Greifswald, was afterwards used extensively for combating plagues of mice which threatened to destroy the harvests in Thessaly (1882) and elsewhere. Loeffler was the first to show experimentally that animals which have recovered from a bacterial disease (mouse-septicaemia) are immune from a second infection with the same organism that caused the disease, in a manner corresponding to what was known for non-bacterial diseases (smallpox, measles, scarlatina). In 1895, with Abel, he demonstrated the formation of specific protective substances in the blood of animals treated with *B. typhosus* and *B. coli*, and that partially positive reactions may be obtained with non-homologous sera owing to these bacilli being related. In 1897 he was made Chairman of the German Commission for the investigation of *foot-and-mouth disease* and, with Frosch and Uhlenhuth, carried out extensive experiments thereon which were published in a series of reports that appeared during 1897–1905. Loeffler and Frosch were the first to discover, in this connection, the existence in animals of a disease due to a provedly ultra-microscopic virus. Loeffler and his collaborators were able to produce a certain amount of immunity to foot-and-mouth disease in experimental animals by inoculating them with a mixture of recovered-serum plus virus; they hyperimmunized horses and cattle with virus maintained in young pigs, thereby obtaining a protective serum from the treated animals which rendered susceptible sheep, pigs and cattle in a measure immune for some weeks against naturally acquired foot-and-mouth disease.

Bacteriological technique is greatly indebted to Loeffler for many of its standard methods. Every tiro in bacteriology is familiar with "Loeffler's alkaline methylene-blue" which is still universally used, and has heard of

"Loeffler's fagella staining method" (1889-90) if he has not actually employed it. It was Loeffler who introduced meat-juice peptone-gelatin, the malachite-green selective medium for the cultivation of *B. typhosus*, and the method of "enrichment" of the numbers of faecal bacteria prior to isolation in pure culture that is used in all bacteriological laboratories, etc.

Besides the foregoing contributions, Loeffler published numerous papers on disinfection (the first in 1881, on steam disinfection, with Koch and Gaffky), milk hygiene, sewage disposal, the bacteriology of water, besides many reports and contributions on these and allied subjects to learned societies, Congresses and Governments.

In 1887 he published a very valuable work, *Vorlesungen über die geschichtliche Entwicklung der Lehre von den Bacterien* (Leipzig: F. C. W. Vogel), which he had hoped to continue from the date 1878 down to the present time, but other engrossing duties rendered this impossible. This book is a well of information, as its title indicates, on the historical development of the science of bacteriology from remote times down to close on 1881. Likewise in 1887, with Uhlwurm and Leuckart, he founded the *Centralblatt für Bakteriologie und Parasitenkunde*, a journal which has flourished ever since.

The value of Loeffler's services was recognized by the conferment upon him of numerous honorary degrees by universities and decorations by Governments of different countries. He was a Privy Councillor and a Member of the German Imperial Council of Health as well as of numerous other bodies.

\* \* \*

Loeffler was the pupil of a number of distinguished teachers of whom may be singled out Reichert, du Bois-Raymond, A. W. Hoffman, Virchow, Traube, Frerichs, v. Bardeleben, v. Langenbeck and Robert Koch. The latter, who was Loeffler's senior by nine years, was called to the Gesundheitsamt in 1880, a year after Loeffler, and until 1884 they were closely associated. Writing of this period (1880-84) in the year 1903, on the occasion of the 60th anniversary of Robert Koch's birth, Loeffler expressed himself with warm appreciation: "The memory of those days, when we still worked in this room, Koch in the centre and we about him, when almost daily new wonders in bacteriology arose before our astounded vision, and we, following the brilliant example of our chief, worked from morn to eve and scarcely had regard to our bodily needs—the memory of that time will remain unforgettable to us. Then it was that we learnt what it means to observe and work accurately and with energy to pursue the problem laid before us." (Fairly literal translation.) The spirit expressed in the foregoing quotation breathed in all the work of Loeffler. His work throughout was characterized by thoroughness and in consequence it has stood the test of time. He published relatively little because he held himself to task until his work on a given theme was as complete as he could make it. A great deal of his work will never see the light because of this. Thus, he carried on researches on immunization against tuberculosis but did

not publish his results because he deemed them inconclusive, although the work had occupied him for years.

He was a man of vigorous physique and great energy, a ready and exceptionally clear speaker whose utterance could be heard distinctly by the largest audience. Under a somewhat rough external manner he bore a modest and kindly nature which endeared him to many.

The accompanying portrait of Loeffler, which is remarkably good, is reproduced from a photograph received from him in 1907.

The following letter from Loeffler was received by me when engaged in editing *The Bacteriology of Diphtheria* in conjunction with my friend Dr Graham-Smith. The letter expresses the writer's regret at his delay in forwarding his manuscript for Chapter 1, but, apart from this, the letter is of interest because of its reference to cholera and to the researches he was then conducting on foot-and-mouth disease, a malady that is to-day causing so much havoc in this country.

*See facsimile<sup>1</sup> of letter from Professor F. Loeffler to G. H. F. Nuttall on opposite page.*

GREIFSWALD, den 8. November 1905.

Hochgeehrter Herr College!

Auf das lebhafte bedauere ich es, dass ich mit meiner Diphtherie Arbeit habe in Rückstand bleiben müssen. Ein unglücklicher Stern hat darüber gewaltet. Als zeitiger Dekan der Fakultät bin ich sehr in Anspruch genommen, meine Maul- und Klauenseuche-Untersuchungen haben viel Zeit erfordert. Ich musste sie auf dem internationalen tierärztlichen Congresse in Budapest vortragen. Nach der Rückkehr wollte ich energisch an die Diphtherie Arbeit gehen. Aber dann kam die Cholera. Material von allen verdächtigen Fällen aus Pommern erhielt ich zugesandt, so dass ich von früh bis spät damit zu thun hatte. Jetzt ist die Cholera vorüber und nunmehr habe ich mich wieder an die Diphtherie-Arbeit gesetzt. Ich bitte nun noch einige Wochen mit mir Geduld zu haben.

Mit freundlichen collegialen Grüissen

Ihr ganz ergebener

(signed)

L. LOEFFLER.

*Translation:*

I greatly regret that I have been obliged to delay my diphtheria work. An unlucky star has hovered over it. At present, as Dean of the Faculty, I am very occupied—my foot-and-mouth investigations have demanded much time. I had to speak of them at the International Congress of Veterinary Medicine in Budapest. On my return, I wished to take up the diphtheria work energetically. But then came the cholera. Material from all suspicious cases was sent to me from Pomerania, so that I was occupied with it from morning till night. Now the cholera has passed and now I have sat down again to the diphtheria work. I beg you therefore to have patience with me for still a few weeks<sup>2</sup>.

<sup>1</sup> Reduction by 1/3

<sup>2</sup> MS. received 16th January, 1906

Greifswald, den 8 November 1905.

Respected Dear College!

Auf das letzte bestrebe  
wir es, das wir mit unserer  
ökonomische Arbeit, welche im Druck  
stand weiter machen. Ein un-  
glücklicher Herr hat darüber  
geworfen. Als Zeitungen bekam  
der Fakultät bis in sehr in  
Reserve genommen, meine Nach-  
richt Klasseweise. Untersuchungen  
wurden nicht gestattet. Ich  
wurde sie auf dem nächsten  
jedes Monatsdienstag  
in Budapest vortragen. Und  
der Minister wollte ich angehört  
an die ökonomische Arbeit gehen  
aber dann kam die Theorie.  
Merkwürdig von allen verdächtigen

Fällen aus Pomeron arbeite ich  
zugezogen, so das ich vor frisch  
bis spät damit zu ihm kam.  
Tatsächlich die Theorie vor mir und  
wurden habe ich mich wieder  
an die ökonomische Arbeit gestellt.  
Ich habe nun vor einigen Wochen  
nur mir Geduld zu haben.

With friendliest regards  
Given The gray envelope  
F. Lüttich

## REFERENCES.

In writing the foregoing biography of Loeffler, I have referred to original notes and publications besides the following sources of information: (a) *Medizinisches Deutschland* (Berlin-Charlottenburg: Adolf Eckstein, 1902), a reprint from the folio volume having been sent to me by Loeffler in 1907, with numerous MS. additions up to that date. (b) *The Bacteriology of Diphtheria*, edited by Nuttall and Graham-Smith (Cambridge: University Press, 1908), where the portrait here reproduced first appeared. (c) Notices that appeared in 1915 from the pens of Abel (*Centralbl. f. Bakteriol. u. Parasitol. Orig.* vol. LXXVI. pp. 241-5) and G. Gaffky (*Deutsche med. Wochenschr.* pp. 393-5, with portrait).



FRIEDRICH LOEFFLER

1852-1915

